Acta Medica Okayama

Volume 39, *Issue* 4 1985 *Article* 1

AUGUST 1985

The calcium antagonist, nicardipine, inhibits antigen-stimulated and anti-IgE-induced histamine release from basophilic leucocytes of atopic asthmatics.

Yoshiro Tanizaki[*] Haruki Komagoe[†] Hiroshi Morinaga[‡]
Jun Ohtani[**] Saburo Nakagawa[††] Masanori Maeda[‡‡]
Hikaru Kitani[§] Kiyoshi Takahashi[¶] Ikuro Kimura[‖]

[*]Okayama University,
[†]Okayama University,
[‡]Okayama University,
[**]Okayama University,
[††]Okayama University,
[‡‡]Okayama University,
[§]Okayama University,
[¶]Okayama University,
[‖]Okayama University,

The calcium antagonist, nicardipine, inhibits antigen-stimulated and anti-IgE-induced histamine release from basophilic leucocytes of atopic asthmatics.*

Yoshiro Tanizaki, Haruki Komagoe, Hiroshi Morinaga, Jun Ohtani, Saburo Nakagawa, Masanori Maeda, Hikaru Kitani, Kiyoshi Takahashi, and Ikuro Kimura

Abstract

The inhibitory effect of nicardipine, a calcium antagonist, on the antigen- and anti-IgE-induced histamine release from basophilic leucocytes of patients with bronchial asthma was examined. The agent significantly inhibited both antigen-stimulated and anti-IgE-induced histamine release from basophils (the maximum percent inhibition was 57.8 +/- 7.2% and 56.0 +/- 8.8%, respectively). Pre-incubation of basophils with nicardipine for periods of up to 120 min did not alter the inhibitory effect. These results suggest that nicardipine modifies the histamine release from basophils which closely participate in an attack of bronchial asthma.

KEYWORDS: histamine release, basophils, antigen, anti-IgE, Ca^{2+} antagonist

---

*PMID: 2413722 [PubMed - indexed for MEDLINE]

Acta Med. Okayama 39, (4), 247-251 (1985)

THE CALCIUM ANTAGONIST, NICARDIPINE, INHIBITS ANTIGEN-STIMULATED AND ANTI-IGE-INDUCED HISTAMINE RELEASE FROM BASOPHILIC LEUCOCYTES OF ATOPIC ASTHMATICS

Yoshiro TANIZAKI, Haruki KOMAGOE, Hiroshi MORINAGA, Jun OHTANI*
Saburo NAKAGAWA*, Masanori MAEDA*, Hikaru KITANI*
Kiyoshi TAKAHASHI* and Ikuro KIMURA*

Department of Medicine, Okayama University Medical School, Misasa Medical Branch and Second Department of Medicine, Okayama University Medical School

Received November 21, 1984

Abstract. The inhibitory effect of nicardipine, a calcium antagonist, on the antigen- and anti-IgE-induced histamine release from basophilic leucocytes of patients with bronchial asthma was examined. The agent significantly inhibited both antigen-stimulated and anti-IgE-induced histamine release from basophils (the maximum percent inhibition was $57.8 \pm 7.2\%$ and $56.0 \pm 8.8\%$, respectively). Pre-incubation of basophils with nicardipine for periods of up to 120 min did not alter the inhibitory effect. These results suggest that nicardipine modifies the histamine release from basophils which closely participate in an attack of bronchial asthma.

Key words : histamine release, basophils, antigen, anti-IgE, Ca^{2+} antagonist.

The inhibition by calcium antagonists of IgE-mediated release of chemical mediators (histamine and SRS-A) from target cells has aroused considerable attention as a possible factor in their antiallergic action. In such IgE-mediated reactions, phospholipid methylation induced by the bridging of IgE molecules on the cell membranes is followed by intracellular influx of calcium ions, which leads to the release of chemical mediators (1, 2). Therefore, in this reaction system, an increase in the intracellular uptake of calcium ions precedes the antigen-stimulated or anti-IgE-induced release of chemical mediators (2-5). This, in turn, implies that the release of these mediators may be prevented by blocking the intracellular influx of calcium ions. The authors previously reported that nifedipine, a calcium antagonist, significantly inhibited the Ca^{2+} influx into, and the histamine release out of, rat mast cells induced by various stimulating agents (6). Although some investigators have discussed the inhibition of histamine release from mast cells by calcium antagonists such as verapamil and nifedipine (7-9), there are only a few reports on the effectiveness of calcium antagonists in blocking the release of chemical mediators from basophils (10), and no reports about inhibition by nicardipine.

In the present study, the inhibitory effect of nicardipine hydrochloride, a calcium antagonist (11), on the antigen-stimulated and anti-IgE-induced histamine

release from basophils was evaluated.

SUBJECTS AND METHODS

Five patients with atopic bronchial asthma, all showing specific sensitivity against house dust (RAST score 2+ or higher) were chosen as the subjects of the histamine release experiments.

Histamine release from basophils was carried out by the whole blood method described in our earlier report (12). Heparinized venous blood (2 ml) was mixed with Hanks' BSS (2 ml) containing various concentrations of nicardipine hydrochloride, and pre-incubated at 37℃. In the time-course study, basophils were pre-incubated with nicardipine for periods of 0, 15, 30, 60 and 120 min prior to antigen challenge. After the pre-incubation, either house dust or anti-IgE (0.2 ml) was added to the treated samples. The histamine content of the cells and supernatant fluid was analyzed by an automated spectrofluorometric histamine analysis system (Technicon). The release of histamine was expressed as a percentage of the total histamine content.

RESULTS

Pre-incubation of basophils with nicardipine for periods of up to 120 min did not significantly increase the inhibitory effect, although the effect seemed to reach a peak at 30 min (Fig. 1). In the following experiments, basophils were pre-incubated with nicardipine for 30 min.

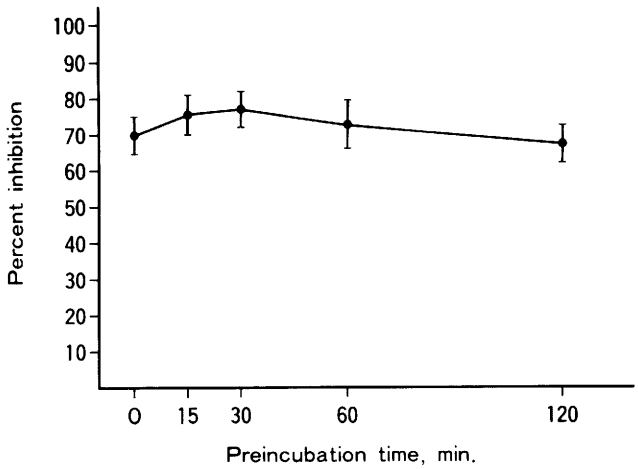

Fig. 1. Effect of the pre-incubation time with nicardipine on antigen-induced histamine release from basophilic leucocytes of atopic asthmatics. Horizontal bars represent the SEM for five subjects.

Percent histamine release from basophils stimulated by house dust was 43.5 ±3.1% (mean ± SE; range 33.9-53.4%). This demonstrates that house dust extract induced a significant amount of histamine release from basophils of each patient. Nicardipine inhibited the release of histamine from basophils dose-

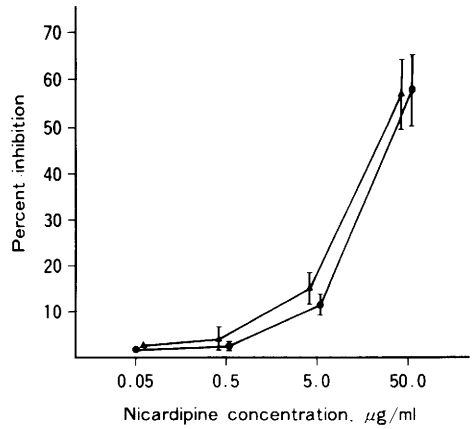

Fig. 2. Inhibitory effects of nicardipine on antigen (●——●)-stimulated and anti-IgE (▲——▲)-induced histamine release from basophilic leucocytes of atopic asthmatics. Horizontal bars represent the SEM for five subjects.

dependently through the concentration range of 0.05-50 μg/ml.

Anti-IgE also induced a significant histamine release from basophils (26.2± 3.1 %), which was inhibited by nicardipine in a dose-dependent manner (Fig. 2). These results indicate that nicardipine exerts a significant inhibitory effect on IgE-mediated histamine release from basophils.

DISCUSSION

In recent years, attention has been directed to the application of calcium antagonists to the treatment of bronchial asthma, in which bronchial hypersensitivity toward various stimulants and antigen-induced release of chemical mediators from target cells are observed. These antagonists, which control smooth muscle contraction and the secretory process of target cells by preventing calcium influx, may be effective in the treatment of the disease. In fact, considerable benefits from calcium antagonists in exercise-induced asthma (13-15) as well as in bronchial hyper-reactivity against histamine (16, 17) have been reported. It is still difficult, however, to determine whether the inhibitory effect of these agents on the occurrence of bronchial asthma is ascribable to the prevention of the release of chemical mediators from target cells or to the suppression of smooth muscle contraction.

In our previous study (6), calcium influx and histamine release from mast cells induced not only by antigen but also by stimulating agents such as concanavalin A, compound 48/80 and Ca ionophore A23187 were significantly inhibited by the calcium antagonist nifedipine. A comparison between nifedipine and sodium cromoglycate revealed that while the former inhibited the ^{45}Ca uptake by mast cells more strikingly than the histamine release induced by antigen stimulation,

the latter affected the two processes similarly. The anti-allergic effect of disodium cromoglycate was ascribed to the blocked calcium influx into mast cells (18). Although the overt effects of the both agents on IgE-mediated release of histamine from target cells seem to be nearly identical, the above results suggest differences in the mechanisms by which they take place.

There are several reports about the inhibitory effect of calcium antagonists on histamine release from mast cells. Ennis, *et al.* (7) reported that verapamil and nifedipine inhibited the release of histamine from rat mast cells stimulated by various agents. The results obtained in the present study are in general agreement with the results described by Ennis, *et al.*, although the cells used for the experiments were different. Furthermore, in both experiments, high concentrations of calcium antagonists were required to produce the inhibitory effect. Saeki, *et al.* (8) and Suzuki, *et al.* (9) also found an inhibitory effect of verapamil on histamine release from rat mast cells.

Although studies on the inhibition of histamine release from mast cells by calcium antagonists have yielded fairly uniform results, no consistent observations have been made on their effect on the histamine release from basophils. Middleton, *et al.* (19) reported that neither verapamil nor nifedipine inhibited the antigen-induced histamine release from basophils. On the other hand, Jensen, *et al.* (10) have shown that verapamil and nifedipine significantly inhibit histamine release from human basophils by antigen, anti-IgE and Ca ionophore A23187. The difference in the effect of the calcium antagonists on basophil histamine release might partially depend on the drug concentrations used in the respective experiments. The results obtained here are in agreement with the results reported by Jensen *et al.*, suggesting that calcium antagonists such as verapamil, nifedipine and nimodipine inhibit basophil histamine release induced by antigen and anti-IgE.

REFERENCES

1. Hirata, F. and Axelrod, J.: Phospholipid methylation and biological signal transmission. *Science* **209**, 1082-1086, 1980.
2. Ishizaka, T., Hirata, F., Ishizaka, K. and Axelrod, J.: Stimulation of phospholipid methylation, Ca^{2+} influx and histamine release by bridging of IgE receptors on rat mast cells. *Proc. Natl. Acad. Sci. USA* **77**, 1903-1906, 1980.
3. Foreman, J.C., Hallett, M.B. and Mongar, J.L.: The relationship between histamine release and ^{45}Ca uptake by mast cells. *J. Physiol.* **271**, 193-214, 1977.
4. Ranadive, N.S. and Dhanari, N.: Movement of calcium ions and release of histamine from rat mast cells. *Int. Arch. Allergy Appl. Immunol.* **61**, 9-18, 1980.
5. Tanizaki, Y. and Townley, R.G.: Effect of BSA on Ca^{2+} influx in mast cells stimulated by ovalbumin. *Int. Arch. Allergy Appl. Immunol.* **70**, 143-145, 1983.
6. Tanizaki, Y., Akagi, K., Lee, K.N. and Townley, R.G.: Inhibitory effect of nifedipine and cromolyn sodium on skin reactions and ^{45}Ca uptake and histamine release in rat mast cells induced by various stimulating agents. *Int. Arch. Allergy Appl. Immunol.* **72**, 102-109, 1983.
7. Ennis, M., Ind, P.W., Pearce, F.L. and Dollerry, C.T.: Calcium antagonists and histamine secre-

tion from rat peritoneal mast cells. *Agents Actions* **13**, 144-148, 1983.

8. Saeki, K. and Kurose, M.: Histamine release from rat mast cells sensitized with mouse antiserum. *Agents Actions* **11**, 98-100, 1981.
9. Suzuki, T., Mori, K. and Uchida, M.: Inhibition by calcium influx of rat mast cells: Difference between induction of histamine release by concanavalin A and compound 48/80. *Eur. J. Pharmacol.* **85**, 155-161, 1982.
10. Jensen, C., Stahl-Skoozn, P. and Norm, S.: Inhibitory effect of Ca antagonist on histamine release from human leucocytes. *In vivo* and *in vitro* experiments. *Allergy* **38**. 233-237, 1983.
11. Endo, M., Yanagisawa, T. and Taira, N.: Dissociation of cyclic AMP and contractile responses to isoprenaline: effects of a dihydropyridine derivative, nicardipine (YC-93), on canine ventricular muscle. *Eur. J. Pharmacol.* **67**, 225-233, 1980.
12. Tanizaki, Y., Komagoe, H., Morinaga, H., Kitani, H., Goda, Y. and Kimura, I.: Allergen- and anti-IgE-induced histamine release from whole blood. *Int. Arch. Allergy Appl. Immunol.* **73**, 141-145, 1984.
13. Barnes, P.J., Wilson, N.W. and Brown, M.J.: A calcium antagonist, nifedipine, modifies exercise-induced asthma. *Thorax* **36**, 726-730, 1981.
14. Cerrina, J., Denjean, A., Alexandre, G., Lockhart, A. and Douroux, P.: Inhibition of exercise-induced asthma by a calcium antagonist; nifedipine. *Am. Rev. Respir. Dis.* **123**, 156-160, 1982.
15. Patel, K.R. and Kerr, J.W.: Calcium antagonists in experimental asthma. *Clin. Allergy* **12**, 15-20, 1982.
16. Williams, D.O., Barnes, P.J., Vickero, H.P. and Rudolf, M.: Effect of nifedipine on bronchomotor tone and histamine activity in asthma. *Br. Med. J.* **283**, 348-348, 1981.
17. Patel, K.R.: Effect of verapamil on histamine and methacholine-induced bronchoconstriction. *Clin. Allergy* **11**, 441-447, 1981.
18. Foreman, J.C. and Garland, L.G.: Cromoglycate and other anti-allergic drugs; a possible mechanisms of action. *Br. J. Med.* **i**, 820-821, 1976.
19. Middleton, E., Drzewiecki, G. and Triggle, D.: Effects of smooth muscle calcium antagonists on human basophil histamine release. *Biochem. Pharmacol.* **30**, 2867-2869, 1981.